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Review

Emerging roles for diverse intramembrane proteases in plant biology ☆

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ABSTRACT

Progress in the field of regulated intramembrane proteolysis (RIP) in recent years has made its impact on plant biology as well. Although this field within plant research is still in its infancy, some interesting observations have started to emerge. Gene encoding orthologs of rhomboid proteases, site-2 proteases (S2P), presenilin/γ-secretases, and signal peptide peptidases are found in plant genomes and some of these gene products were identified in different plant cell membranes. The lack of chloroplast-located rhomboid proteases was associated with reduced fertility and aberrations in flower morphology. Mutations in homologues of S2P resulted in chlorophyll deficiency and impaired chloroplast development. An S2P was also implicated in the response to ER stress through cleavage of ER-membrane bZIP transcription factors, allowing their migration to the nucleus and activation of the transcription of BiP chaperones. Other membrane-bound transcription factors of the NAC and PHD families were also demonstrated to undergo RIP and relocalization to the nucleus. These and other new data are expected to shed more light on the roles of intramembrane proteases in plant biology in the future. This article is part of a Special Issue entitled: Intramembrane Proteases.

Contents

1. Introduction

Hydrolysis of a peptide bond within the hydrophobic core of a membrane, which seemed initially paradoxical, has been recognized in the past two decades or so as a ubiquitous process occurring in all forms of life. This cleavage is involved in a wide array of biological processes and regulates many different functions. The discovery of different families of intramembrane proteases; rhomboid proteases, site-2 proteases, presenilin/γ-secretases, and signal peptide peptidases, together with the demonstration of their role in signaling, membrane remodeling, protein quality control, cell adhesion and communication has consolidated their fundamental role in development and physiology of eukaryotes and prokaryotes alike. This is evident in this special issue. The progress in the field of regulated intramembrane proteolysis (RIP) in recent years has radiated into plant biology as well. Although the number of reports on RIP in plants is still limited, interesting observations have started to accumulate. The ubiquitous nature of RIP and the enzymes responsible for this process has prompted plant biologists to look for homologs of these enzymes in plants, and to incorporate the concepts associated with RIP into their hypotheses. Independent of these, analysis of specific mutants culminated in the identification of mutations in specific intramembrane proteases as responsible for certain mutant phenotypes. In yet another line of research, potential substrates for intramembrane proteolysis in plants have been identified, although the responsible proteases are still unknown. In the following, and in

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Fig. 1 and Table 1, the limited available information on these subjects is summarized and evaluated.

2. Rhomboid proteases

Rhomboids are widely spread intramembrane serine proteases that are found in nearly all sequenced organisms. They are involved in different biological functions such as signaling, development, apoptosis, organelle integrity, parasite invasion, and more (for recent reviews, see Lemberg, McQuibban, Rather, Sibley, and Lemieux in this issue, and [1]). Of the 16 genes related to rhomboid proteases found in the *Arabidopsis* genome, one belongs to the PARL-type (At1g18600) and three (At1g74130, At1g77860, At5g38510) are expected to be inactive due to lack of conservation in an around the active serine [1,2]. Although the body of literature on plant rhomboids is still small, contradicting nomenclature already exist. For the sake of uniformity, we will use here the nomenclature of Lemberg and Freeman [2], along with the original names in parentheses where relevant.

The occurrence of rhomboid homologs in plants was first mentioned in 2001 [3]. Koonin et al. [4] have then identified *Arabidopsis* sequences containing the conserved active serine and its surrounding residues (GASGA), characteristic of rhomboid proteases. The first report on experimental work with plant rhomboids appeared shortly afterwards [5]. Based on their homology to the *Drosophila* Rho-1, eight sequences were identified in the *Arabidopsis* genome, although their overall sequence similarity was relatively low, less than 20%. Further characterization of two of these, AtRBL1 and AtRBL2 (for *Arabidopsis thaliana* rhomboid-like), revealed that their transcripts accumulated in all tissues, and transient expression assays of GFP-fusions in protoplasts suggested that they located in the Golgi apparatus [5]. Testing their activity in a mammalian cell transfection system demonstrated that AtRBL2, but not AtRBL1, could cleave *Drosophila* substrates, suggesting that at least AtRBL2 is a bona fide rhomboid protease. However, since the known *Drosophila* substrates of Rho-1 do not have homologs in plants, it is believed that rhomboid proteases in plants have their own specific substrates.

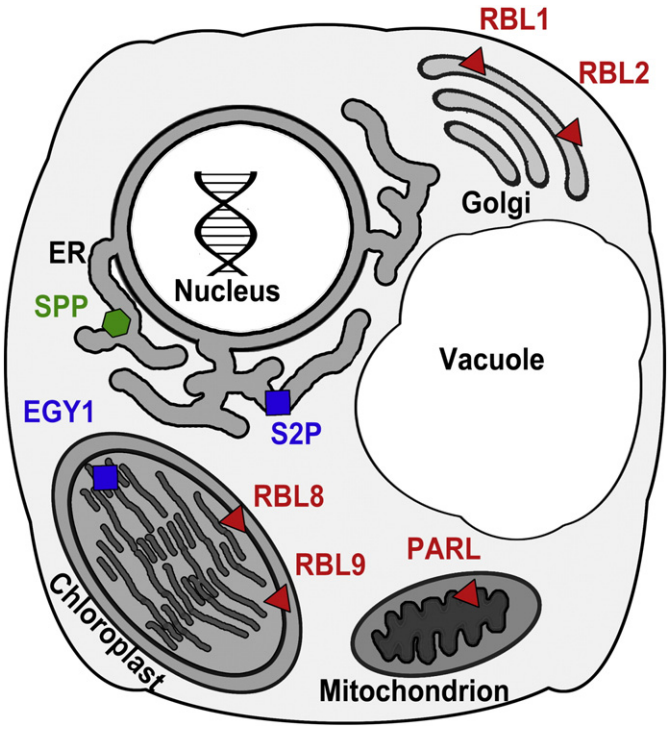

Fig. 1. Identified intramembrane proteases and their cellular location in plant cells. Plant intramembrane proteases whose cellular location was determined are depicted. Rhomboid proteases are colored in red, S2Ps are in blue and SPP in green.

Table 1
Identified plant intramembrane proteases and substrates for intramembrane proteolysis.

Protein	Cellular location	Biological function	Reference
Proteases			
Rhomboid proteases			
AtRBL1	Golgi	Unknown	[5]
AtRBL2	Golgi	Unknown	[5]
AtRBL8	Chloroplast inner envelope	Flower morphology	[8,9]
AtRBL9	Chloroplast inner envelope	Unknown	[7]
AtPARL	Mitochondrion	Unknown	[7]
S2P			
EGY1	Chloroplast thylakoid	Chloroplast development; ABA signaling	[12,14,16]
EGY2	Chloroplast	Hypocotyl elongation	[17]
AraSP	Chloroplast inner envelope	Chloroplast development	[18]
SPP			
AtSPP	ER	Pollen maturation	[19,20]
AtSPPL1 & 2	Endosomes	Unknown	[19]
Substrates			
Transcription factors			
bZIP17,28&60	ER	ER stress response	[24–28]
NTM1	Microsomes	Cytokinin signaling	[31]
NTL8	Plasma membrane	Salt-responsive flowering	[32]
PHD	Chloroplast envelope	Chloroplast-nucleus signaling	[35]

Reasoning that diverse rhomboid substrates have in common two features, a single trans-membrane domain and a large soluble domain, Karakasis and co-workers [6] attempted to link between Tic40, a component of the protein import machinery into chloroplasts, and one *Arabidopsis* rhomboid-like protein. Using a mitochondria-based system, they showed that Tic40 could be processed by the product of the At1g74130 gene, suggesting a role for this protein in the biogenesis of the chloroplast protein import machinery. Nevertheless, this suggestion is debatable, as the product of the aforementioned gene lacks the conserved catalytic serine and histidine residues, and thus is expected to be proteolytically inactive [1].

Two other *Arabidopsis* rhomboid-like proteases that were studied are AtRBL9 and AtPARL (designated AtRBL11 and AtRBL12 in the original paper) [7]. Transient expression assays of GFP-fusions suggested that these proteins were targeted to chloroplasts and mitochondria, respectively [7]. However, the *Arabidopsis* mitochondrial rhomboid failed to complement the corresponding yeast mutant, and did not recognize the yeast substrates cytochrome *c* peroxidase and a dynamin-like GTPase.

More recently, AtRBL8 was also identified in chloroplasts, and was located to the envelope membrane [8]. Interestingly, the *Arabidopsis* mutant lacking this protein demonstrated reduced fertility and aberrant flower morphology [9]. Proteomic analysis of a double mutant lacking both AtRBL8 and AtRBL9 revealed that in the absence of these two rhomboid proteases the level of allene oxide synthase (AOS) was affected, although it was not determined which of these two was responsible for this effect [8]. As AOS is involved in the synthesis of the plant hormone jasmonic acid, this observation provides a link between the lack of chloroplast rhomboid proteases and the morphologic phenotype. Another interesting observation was that AtRBL9 forms homo-oligomers [8]. Although the functional significance of rhomboid oligomerization is still unknown, it is interesting to note that bacterial rhomboids were recently reported to oligomerize as well [10].

3. Site-2 protease (S2P)

S2Ps belong to a large family of metalloproteases, found in many different eukaryotic and prokaryotic organisms, where they are

involved in stress response, cell division, bacterial mating, pathogenesis, and more. For most recent reviews, see [11] and reviews by Kroos and Akiyama, Glickman, and Rawson in this issue.

A genetic screen for *Arabidopsis* mutants displaying reduced chlorophyll accumulation and deficiency in ethylene-induced gravitropism revealed EGY1, a 59-kDa membrane-bound metalloprotease homologous to S2P, located in the chloroplast [12]. It contains eight transmembrane α-helices at its C-terminus and is proteolytically active. Although the intraorganellar location of EGY1 was not determined in that work, it was identified in thylakoid membranes in proteomic studies (see the Plant Proteomics Database, PPDB, [13]; http://ppdb.tc.cornell.edu). Mutant plants had reduced levels of grana stacking and light-harvesting complex (LHC) proteins, suggesting that this protease is required for proper chloroplast development [12]. In the absence of EGY1, pleiotropic effects were observed also in size and number of plastids, as well in ethylene-dependent gravitropic growth [14]. More recently, analysis of an *Arabidopsis* mutant hypersensitive to NH_4^+ stress revealed a mutation in the gene encoding EGY1 as responsible for this phenotype [15]. Moreover, it appears that EGY1 integrates abscisic acid (ABA) signaling to regulate the expression of NH_4^+-responsive genes, although it is not known how. The chlorophyll-deficient phenotype of the tomato mutant *lutescent2* was recently also attributed to an EGY1 ortholog [16], supporting the proposed role of the protease in chloroplast development. However, mechanistic insights into this process are still missing.

Sequence comparisons of the *Arabidopsis* EGY1 protease revealed that it belongs to a larger family containing at least four more members: EGY2, AraSP, At1g05140 and At4g20310 [17]. EGY2 resides in chloroplasts, contains seven trans-membrane domains, and is like EGY1, the recombinant protein degrades β-casein in vitro. *Arabidopsis* EGY2 knockout plants looked very similar to the wild type, however, their hypocotyls were somewhat shorter, and the level of their fatty acids was lower [17]. The other S2P-related protein, AraSP, was localized to the *Arabidopsis* chloroplast inner-envelope membrane [18]. Antisense and T-DNA insertion lines of this protease demonstrated severely impaired chloroplast biogenesis. Nevertheless, similar to mutants of EGY1, how these proteases are involved in chloroplast biogenesis is not clear.

4. Signal peptide peptidase (SPP)

The aspartic protease SPP is another protein that belongs to the class of intramembrane proteases. In all eukaryotes studied, it is located in the ER membrane, with its N- and C-termini exposed to the lumen and the cytosol, respectively. Its active site sequences include YD and GXGD and its substrates are type II membrane signal peptides that need to be processed (see [18,19] and the reviews of Fluhrer and Sibley in this issue). The *Arabidopsis* genome contains six orthologs of SPP, designated AtSPP and AtSPPL1-5 (for SPP-like) [19]. Transcripts of AtSPP and AtSPPL1-3 were found in all tissues whereas those of AtSPPL4 and 5 were undetectable. Expression of SPP-GFP fusions revealed that AtSPP localizes to the ER, and AtSPPL1 and 2 reside in endosomes [19]. First insight into the physiological role of these proteins was obtained by studying *Arabidopsis* knockout lines of AtSPP [20]. These turned out to be impaired in pollen maturation and development. Here again, the protein was localized to the ER membrane, but neither its substrates nor its mode of action is known. At least three SPP-like genes are found in the genome of the legume *Medicago truncatula*, where the involvement of one of them in nodule development is suggested [21].

5. Presenilin/γ-secretase

The least studied intramembrane protease in plants to date is presenilin/γ-secretase. Presenilin/γ-secretases are aspartyl proteases that cleave type I substrates within their trans-membrane domains to release C- and N-terminal peptides. Their catalytic aspartate residues are found within the conserved sequence of YD/GxGD [22]. The *Arabidopsis* genome contains two genes encoding presinilins, whereas the genome of the moss *Physcomitrella patens* contains only one. Knocking out the moss gene resulted in pleotropic phenotypic defects, including straight instead of curly filament growth, which could be linked to impaired function of the cytoskeleton [23]. The WT phenotype could be rescued by expression of either the WT presinilin protein or its proteolytically-inactive variant, suggesting that the activity of presinilin in this model is independent of γ-secretase [23]. However, the mechanistic details of this phenomenon are yet to be deciphered.

6. RIP substrates

In 2007 Liu et al. have reported on what appears to be the first two documented cases in plants, where RIP substrates, their sub-cellular location and the relevant protease were described [24,25]. Upon treatment of *Arabidopsis* plants with tunicamycin, an inhibitor of N-linked protein glycosylation, they observed in vivo processing of the ER membrane-bound bZIP28 transcription factor. This cleavage releasing the N-terminal half of the protein into the cytoplasm allowed its translocation to the nucleus. This in turn elicited upregulation of expression of ER stress response genes [24]. Consistent with this observation, expression of a truncated, soluble bZIP28 resulted in constitutive expression of the same genes without tunicamycin treatment [24,26]. Although the protease responsible for this processing event was not identified, bZIP28 contains the canonical site for the subtilisin-like serine protease S1P in the lumen-facing C-terminus of the protein, as well as a putative S2P site on its cytosolic side [24]. Whether S1P is required for this process or not, it is likely that a S2P ortholog mediates the release of the bZIP domain-containing N-terminus from the membrane. Salt stress response, which may be considered as a kind of folding stress, also involves a similar mechanism, though using a different transcription factor, bZIP17. In this case, inactivation of the genes encoding either the transcription factor itself or the S1P protease eliminated the upregulation of salt-stress responsive genes [25], strengthening the notion that RIP has important roles in plants as well.

Another substrate of RIP is bZIP60. Accumulation of this membrane-bound transcription factor is enhanced by drugs eliciting ER stress response, like tunicamycin, DTT and azetidine-2-carboxylate [27]. Expression of the soluble domain of this protein resulted in its accumulation in the nucleus and activation of transcription of BiP proteins—the ER chaperones of the HSP70 family, which are typical of ER stress response. Further studies demonstrated that *Arabidopsis* knockout lines show weaker induction of several but not all ER stress-responsive genes [28]. For instance, BiP1 accumulates in the knockout lines just like in wild type, where accumulation of BiP3 is totally dependent on the presence of bZIP60. It was also shown that this protein is located in the ER, upon induction of ER stress it is proteolytically processed, and its N-terminal domain relocates to the nucleus [28]. Using S1P and S2P mutants (in the At5g19660 and At4g20310 genes, respectively), these authors showed that these gene products were not involved in the processing step. Nevertheless, one cannot rule out the possibility of redundancy, at least in the case of S2Ps, as another gene product (At1g05140) might compensate for the loss of the first one.

In addition to bZIP, other plant transcription factors are expected to be targets of RIP. In fact, more than 10% of all *Arabidopsis* transcription factors are predicted to locate in membranes, including those from the NAC family [29,30], and hence their activity requires liberation from the respective membrane, probably by proteolytic processing. One such protein, NTM1, is cleaved and mediates cytokinin signaling during cell division [31]. In its full-length form, this protein is detected in the microsome fraction, but neither the exact membrane it associates with nor its processing peptidase is known yet. Another NAC transcription factor, NTL8, is located in the plasma membrane. Its proteolytic processing represses flowering of *Arabidopsis*, and the processing appears

to be induced by high concentrations of salt [32]. Here again, the processing enzyme is still unknown.

Communication between the chloroplast and the nucleus is essential for the biogenesis and function of the chloroplast. This has been the subject of intensive studies over the past two decades; however, the nature of the molecular relay has remained elusive (for review, see [33,34]). A major breakthrough in the field was the recent identification of a chloroplast envelope-bound PHD transcription factor that possesses transmembrane domains. Upon proteolytic cleavage, the soluble N-terminal domain of this protein is released from the membrane and relocates to the nucleus, where it activates the transcription of the ABA response gene ABI4 [35]. The protease involved in this process is still unknown, but it is most likely one of the intramembrane proteases capable of cleaving within transmembrane α-helices.

7. Conclusion

Of the different intramembrane proteases and roles in plant biology described above, it appears that the RIP process best characterized is the ER stress response. It is quite well established now that upon such stress, bZIP transcription factors embedded in the ER membrane are released, relocated to the nucleus, and activate the transcription of BiP chaperones that function in the lumen of the ER. Circumstantial evidence suggests that S2P is the protease involved in this process, but this needs to be further confirmed. Furthermore, how the presence of ill-folded protein in the ER is sensed, and the signal transduced to induce proteolytic cleavage is an enigma. Other membrane-bound transcription factors, of the NAC and PHD families, have also been documented to be involved in intracellular signaling in plants. However, the proteases involved in their cleavage are still obscure.

The occurrence of S2Ps in plants and their importance for proper development of chloroplasts are also established, but mechanistic details of their involvement are unknown. Similarly, the presence of rhomboid proteases and SPPs in different plant cellular membranes was demonstrated, but their link with developmental processes or other responses is still weak. These are expected to be the subjects of future studies, and together with studies originating from deciphering the genetic and molecular basis for specific phenotypes in different mutants, will most likely shed more light on the roles of intramembrane proteases in plant biology.

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